

Targeted Research Area: Neurodevelopment & Biobehavioral Development

General Information on Neurodevelopment & Biobehavioral Development

- **Prevalence and incidence of disorders related to Neurodevelopment: & Biobehavioral Development**
 - Approximately 1% of all children are mentally retarded.
 - Estimated that nearly 12 million children in the United States under age 18 suffer from one or more learning, developmental, or behavioral disabilities.⁵⁷
 - Attention deficit hyperactivity disorder (ADHD) affects 3%-6% of all school children, though recent evidence suggests prevalence as high as 17%. Children taking Ritalin for ADHD has doubled every 4-7 years since 1971; an estimated 1.5 children are on Ritalin.⁵⁸
 - Learning disabilities affect an estimated 5-10% of children in public schools.⁵⁹
- **Mortality from Neurodevelopment and Biobehavioral Development Disorders:** This information was not readily available to Lewin.
- **Disease severity/disease burden:** Though trivial on an individual level, when applied across populations, neurotoxicants have a significant impact. A loss of 5 points in IQ is of minimal significance in a person with an average IQ. However, a shift of 5 IQ points in the average IQ of a population of 260 million increases the number of functionally disabled by over 50% (from 6 to 9.4 million).⁶⁰
- **Cost to individual/family/society/healthcare system:** Evokes broader questions about career and educational opportunities and how effects of toxicology can affect social class. Societal and economic benefits are considerable as there can be reductions in poverty, welfare, crime, and high school dropouts, and increases in earnings.⁶¹
- **Frequency/load of exposure:** This information was not readily available to Lewin.
- **Special Populations:** This information was not readily available to Lewin.

Hypotheses 19 – 27, described on the following pages, are associated with the Neurodevelopment and Biobehavioral Development targeted research area.

⁵⁷ Schettler T, Stein J, Reich F, et al. In harms way: Toxic threats to child development. Greater Boston Physicians for Social Responsibility 2000.

⁵⁸ Ibid.

⁵⁹ Ibid.

⁶⁰ Ibid.

⁶¹ Weiss B. Vulnerability of children and the developing brain to neurotoxic hazards. Environmental Health Perspectives 2000;108:375-81.

Hypothesis #19: Organophosphate pesticides such as PCBs, PCDDs, and PCDFs have a detrimental impact on neurodevelopment, causing functional, neurologic, and cognitive expression.

General Information Related to Hypothesis #19

- **Frequency/load of exposure:**
 - Exposure to organic contaminants begins prior to conception and continues throughout gestation. However, human newborns are exposed to larger amounts of organic contaminants through breast feeding than in any other stage of development or life.⁶²
 - Exposure is universal due to the mode of exposure. PCBs do not biodegrade and thus accumulate in the food chain, and are present in fish, fish products, animal fats, and often pass from the mother to the fetus/newborn through the placenta or breast milk.⁶³
 - Animal studies of lead, mercury, and PCBs each underestimate the levels of exposures that cause effects in humans by 100 to 10,000-fold.⁶⁴
- **Findings from the recent research (targeted search):** Information reported in the following four studies contributed to the above-mentioned hypothesis.

Study #1: Eskenazi B, Bradman A, Castoria R. Exposures of children to organophosphate pesticides and their potential adverse health effects. *Environmental Health Perspectives* 1999;107(3):409-419.

Study #1 hypothesis being tested: Low-level exposure to organophosphate pesticides has potential adverse health effects on children's nervous and respiratory systems.

Study #1 findings: Studying findings are inconclusive. Data neither support nor refute adverse health effects from low-level pesticide exposure. However, evidence available from animal models shows evidence of significant neurodevelopmental effects that link exposure to organophosphate pesticides during gestation and postnatal development to: 1) altered DNA synthesis in the brain, 2) adverse effects on cellular intermediates, 3) decreased motor function, and 4) low birth weight, which may be significant to the development of asthma or determining its severity. Additional research is needed to determine the various sources, pathways and levels of pesticide exposure in children, especially children living in high risk environments such as farms and agricultural communities, and develop effective interventions and minimize pesticide exposure. Additionally, more research is needed to understand whether pesticide exposure could be an important factor in the etiology and morbidity of childhood asthma.

⁶² Feeley M, Brouwer A. Health risks to infants from exposure to PCBs, PCDDs and PCDFs. *Food Additives and Contaminants* 2000 Apr;17(4):325-33.

⁶³ Ribas-Fito N, Sala M, Kovgevinas M, Sunyer J. Polychlorinated biphenyls (PCBs) and neurological development in children: a systematic review. *Journal of Epidemiology and Community Health* 2001; 55: 537-546.

⁶⁴ Schettler T, Stein J, Reich F, et al. In harms way: Toxic threats to child development. *Greater Boston Physicians for Social Responsibility* 2000.

Study #2: Feeley M, Brouwer A. Health risks to infants from exposure to PCBs, PCDDs and PCDFs. *Food Additives and Contaminants* 2000;17(4):325-33.

Study #2 hypothesis being tested: Environmental exposure to a variety of anthropogenic persistent organic chemicals, such as dioxins and PCBs, can cause adverse mental and physical developmental abnormalities.

Study #2 findings: Studies have found detectable concentrations of PCBs and dioxins in amniotic fluid, placenta, and fetal tissue, while breastfed infants were observed having higher levels of toxins in their blood than their mother. Infants exposed in utero were observed to have deficits to their mental and functional development (e.g., lower birth weights, alternations in thyroid hormones, lymphocyte subpopulations, and neurodevelopment). There were more negative effects for infants exposed in utero versus through breastfeeding. Though subtle, the observed neurodevelopment deficits can have unknown consequences related to future intellectual function. Efforts should focus on identification and control of environmental and food chain contamination since in utero exposure is a direct consequence of accumulated maternal body burdens prior to conception.

Study #3: Ribas-Fito N, Sala M, Kovgevinas M, Sunyer J. Polychlorinated biphenyls (PCBs) and neurological development in children: a systematic review. *Journal of Epidemiology and Community Health* 2001;55:537-546.

Study #3 hypothesis being tested: Exposure to organochlorine compounds such as polychlorinated biphenyls hinder neurological development in children.

Study #3 findings: Studies evaluating exposed children showed increase in abnormal reflexes, decrease in motor skills, and deficits in cognitive skills. Review of studies indicates that prenatal exposure to PCBs has subtle adverse effects on child neurodevelopment. However, due to differences in study designs, the degrees of risk associated with neurodevelopmental effects at current levels of exposures (dose-response relation), critical periods of exposure, and the possible reversibility of effects are not established. Also, since exposure is universal, more research should be conducted on populations exposed to organochlorine compounds.

Study #4: Weiss B. Vulnerability of children and the developing brain to neurotoxic hazards. *Environmental Health Perspectives* 2000;108:375-81.

Study #4 hypothesis being tested: Neurobehavioral toxicity of a particular or group of agents can impair brain development and functional expression.

Study #4 findings: Lead is one of a multitude of toxic agents that impact IQ scores, additional factors include: maternal intelligence, family income, education, race, child's environment, etc.). Maternal smoking during pregnancy also lowers IQ of offspring.

Hypothesis #20: Autism is a neurodevelopmental disease that may be linked to components of vaccines and immunizations and may have a genetic link.

General Information Related to Hypothesis #20

- **Prevalence and incidence of autism:**
 - The prevalence of autism estimates run from approximately 1-in-500 children, to 2-in-1000 children.^{65,66}
 - Autism spectrum disorders have increased from 1 in 10,000 in 1978 to 1 in 300 in 1999.⁶⁷
 - Though not as prevalent as other developmental disorders, autism spectrum disorders affect more than 400,000 people in the U.S. The reported number of autism cases is increasing dramatically every year.⁶⁸
 - Within the state of California, the number of children entered into the autism registry increased by 210% between 1987 and 1998.⁶⁹
- **Disease severity/disease burden**
 - Autism is a complex, life-long biological disorder of development that results in social interaction problems, communication difficulties, and restrictive or repetitive interests and behaviors.⁷⁰
 - Autism is one of the most severe developmental brain disorders.⁷¹
- **Special Populations:** Males are three-to-four times more likely to be affected by autism than females; it occurs in all racial, ethnic, and social groups.⁷²
- **Findings from the recent research (targeted search):** Information reported in the following three studies contributed to the above-mentioned hypothesis.

Study #1: Megson MN. Is autism a G-protein defect reversible with natural vitamin A? Medical Hypotheses 2000;54(6):979-983.

Study #1 hypothesis being tested: Autism is linked to the disruption of the Galpha protein, which affects the hippocampal retinoid receptor pathways that are critical for vision, sensory perception, language processing and attention.

⁶⁵ NICHD. *Facts About Autism*. Available at <http://www.nichd.nih.gov/publications/pubs/autism1.htm>

⁶⁶ Schettler T, Stein J, Reich F, et al. In harms way: Toxic threats to child development. Greater Boston Physicians for Social Responsibility 2000.

⁶⁷ Megson MN. Is autism a G-protein defect reversible with natural vitamin A? Medical Hypotheses 2000; 54(6): 979-983.

⁶⁸ London EA, Etzel RA. The environment as an etiologic factor in autism: a new direction for research. Environmental Health Perspectives 2000 Jun;108 Suppl 3:401-4.

⁶⁹ Schettler T, Stein J, Reich F, et al. In harms way: Toxic threats to child development. Greater Boston Physicians for Social Responsibility 2000.

⁷⁰ NICHD. *Facts About Autism*. Available at <http://www.nichd.nih.gov/publications/pubs/autism1.htm>

⁷¹ Ibid.

⁷² Ibid.

Study #1 findings: Study of 60 autistic children suggests that autism may be caused by insertion of a G-alpha protein defect into an already genetically predisposed child (e.g., child with at least one parent with a pre-existing G-alpha protein defect and has night blindness, pseudohypoparathyroidism or adenoma of the thyroid or pituitary gland.) The study found that treatment with natural vitamin A followed by blocked stimulation of acetylcholine receptors for neurotransmitters proved to be promising. Treatment resulted in improved vision, sensory perception, language processing, and increased attention. Recent evidence indicates that autism is a disorder of the nervous and immune system that affects multiple pathway and linked to the disruption of the G protein, affecting pathways of retinoid receptors in the brain.

Study #2: DeStefano F. Vaccines and Autism. Concise Reviews of Pediatric Infectious Diseases. 2001;20(9):887-888.

Study #2 hypothesis being tested: Measles-mumps-rubella (MMR) may be a causal agent of autism as well as other immunization factors such as pertussis immunizations, the thimerosal in vaccines, the receipt of multiple vaccine antigens, maternal peripartum rubella immunizations, and/or to genetic factors.

Study #2 findings: Studies published to date and epidemiologic data from Sweden, Great Britain, and California have not found an association between the MMR vaccine and the development of autism. The Immunization Review Committee of the Institute of Medicine as well as a special panel of the American Academy of Pediatrics both concluded that available evidence does not support this hypothesis. Published data are not available to determine whether autism may be related to other immunization factors such as pertussis immunization, thimerosal in vaccines, receipt of multiple vaccine antigens, maternal peripartum rubella immunizations, and/or to genetic factors.

Study #3: London EA, Etzel RA. The environment as an etiologic factor in autism: a new direction for research. Environmental Health Perspectives 2000;108(Suppl 3):401-4.

Study #3 hypothesis being tested: Environmental exposures during pregnancy could cause or contribute to autism based on their interaction with developmental genes in the fetus.

Study #3 findings: Evidence for environmental origin is circumstantial. The neurobiology of the prenatal developmental process and the environmental exposures that can effect those changes may serve as a clue. Retinoids are one promising area of research; as known modifiers of the Hox genes, retinoids may be a cause of autism because animal models involving retinoic acid have developed and share many of the brain lesions associated with autism including cerebellar malformations, cranial nerve and dopaminergic system abnormalities. Increased geographic clustering surveillance may also yield information linking environmental factors to autism. Though direct evidence for any etiology in autism is lacking, there are ample reasons for environmental research. Autism may be a disease of very early fetal development (approx. 20-24 days of gestation). Additional studies are needed to identify genetic abnormalities, basic neurobiology of the disease, and epidemiological studies.

Hypothesis #21: Stress, neglect, and trauma caused by child abuse and maltreatment have adverse affects on a child's neurodevelopment.

General Information Related to Hypothesis #21

- **Findings from the recent research (targeted search):** Information reported in the following five studies contributed to the above-mentioned hypothesis.

Study #1: Glaser D. Child abuse and neglect and the brain: A review. Journal of Child Psychology and Psychiatry 2000;41(1):97-116.

Study #1 hypothesis being tested: Child abuse and neglect are associated with adverse characteristics of neurodevelopment.

Study #1 findings: Studies demonstrate adverse effects on the brain from child abuse and neglect resulting in stress responses, including deregulation of the hypothalamic-pituitary adrenal axis and parasympathetic and catecholamine responses, and reduction in brain volume. There is evidence for changes in brain function in relation to child abuse and neglect. Child abuse/neglect and brain neglect could have implications on hyperarousal, aggressive responses, dissociative reactions, difficulties with executive functions, and education underachievement problems. Mechanism bringing about these changes need to be further studied, and may be more related to chronic abuse and neglect.

Study #2: Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: Preclinical and clinical studies. Biological Psychiatry 2001;49:1023-1039.

Study #2 hypothesis being tested: Persistent sensitization of the central nervous system as a consequence of early life stress may result in increased vulnerability to subsequent stress and development of depression and anxiety.

Study #2 Findings: Preclinical and clinical studies suggest that early life stress induces long-lived hyperactivity and sensitization of CNS, resulting in behavioral stress responsiveness. Findings from preclinical studies may be comparable to findings in adult patients with mood and anxiety disorders, however, more studies with human subjects exposed to early life stress are needed. There may be a genetic vulnerability to the neurobiological effects of early life stress.

Study #3: De Bellis MD. Developmental traumatology: a contributory mechanism for alcohol and substance use disorders. Psychoneuroendocrinology 2002;27:155-170.

Study #3 hypothesis being tested: Early childhood traumatic experiences are associated with an enhanced risk of adolescent and adult alcohol substance use disorder due to an

enhanced vulnerability for psychopathology, post-traumatic stress disorder (PTSD), and depression resulting from adverse influences on brain development.

Study #3 findings: Review of the literature suggests that childhood maltreatment and the diagnosis of PTSD are associated with an enhanced risk of adolescent and adult alcohol substance use disorders. The adverse influences of maltreatment on major biological stress response systems and brain development may contribute to the enhanced risk of adolescence and adult alcohol and substance abuse disorders. However, studies have relied on cross-sectional analyses of limited data and cannot definitively link the neurobiology of maltreatment-related PTSD with the neurobiology of alcohol and substance use disorders. Further research into the biological sequelae and mechanisms of symptom production in PTSD may help understand environmental-related mechanisms involved in the development of adolescent or young adult onset alcohol or substance use disorders.

Study #4: Bremner JD, Vermetten E. Stress and development: Behavioral and biological consequences. *Development and Psychopathology* 2001;13:473-489.

Study #4 hypothesis being tested: Early stress may have long-term effects on brain structures, affecting memory, learning, and lead to PTSD.

Study #4 findings: Animal models demonstrated that early stressors (during the last trimester of pregnancy) resulted in alternations in the morphological and behavioral development of the offspring and had long-term effects on neurobiology that persisted into adult life. However, the findings do not necessarily translate into human studies due to multiple complex factors such as copresence of neglect, family environment, variations in individual responses to stressors, and personalities. Early stressors to children result in long-term dysregulation of stress response systems and lead to changes in the brain. Studies indicate that childhood abuse has behavioral and biological consequences such as post-traumatic stress disorders. Understanding the effects of early stress on neurobiology provides a basis for studying the effects of childhood abuse on neurobiological development. Stressful environmental events can modify the way in which the genome is transcribed. Stress-induced changes in neurobiology underlie the development of psychopathology in those who do develop psychiatric symptoms. Depression is also an outcome of childhood abuse that affects neurobiological development.

Study #5: Wadhwa PD, Sandman CA, Garite TJ. The neurobiology of stress in human pregnancy: implications for prematurity and development of the fetal central nervous system. *Progress in Brain Research* 2001;133:131-142.

Study #5 hypothesis being tested: Prenatal psychosocial stress, social support, and personality variables may affect neuroendocrine parameters and alter fetal/infant brain development.

Study #5 findings: Results indicate significant associations between prenatal psychosocial factors and maternal neuroendocrine parameters. Psychosocial factors

were associated with increased hormone levels, and a combination of psychosocial and sociodemographic factors accounted for variance in measures of all neuroendocrine parameters in the study. Findings support the premise that maternal-placental-fetal neuroendocrine parameters are associated with features of maternal psychosocial functioning in pregnancy. Maternal psychosocial factors that affect the neuroendocrine system affect pregnancy outcomes and the fetal central nervous system.

Hypothesis #22: Maternal immune response to infections can have an adverse effect on the fetus' neurodevelopment.

General Information Related to Hypothesis #22

- **Findings from the recent research (targeted search):** Information reported in the following study contributed to the above-mentioned hypothesis.

Study #1: Patterson, PH. Maternal infection: window on neuroimmune interactions in fetal brain development and mental illness. *Current Opinion in Neurobiology* 2002;12:115-118.

Study #1 hypothesis being tested: Maternal immune response can influence fetal brain development through circulating cytokines.

Study #1 findings: Mouse models show that respiratory infection in the pregnant mother leads to significant changes in behavior and pharmacology of the offspring, some of which are applicable to schizophrenia and autism. Direct viral infection can have adverse health consequences for the developing fetus. Maternal infections lead to serious consequences for fetus (e.g., miscarriage, premature and still births, early neonatal deaths), and increase risk of mortality for the mother. Need to further study the link between maternal infection and mental illness. Also relevant for investigating potential therapies. More research about cytokines and corticosteroid levels is needed to better understand neuroimmune interactions.

Hypothesis #23: In utero and postnatal exposure to methylmercury has adverse effects on a child's neurodevelopment and biobehavioral development.

General Information Related to Hypothesis #23

- **Frequency/Load of exposure to mercury:**
 - According to the EPA, the highest emitters of mercury to the air include coal-burning power plants, municipal waste combustors, medical waste incinerators, and hazardous waste combustors. Emissions from these facilities gets deposited in water and land.
 - Human exposure to methylmercury primarily occurs through eating contaminated fish. Women of childbearing age who are exposed to methylmercury through consumption of contaminated fish are at a higher risk for health effects. As of July 2000, 40 states had issued fish consumption advisories due to contamination by mercury.⁷³
- **Cost to individual/family/society/healthcare system :**
 - Differences in IQ have been associated with difference in educational achievement and average lifetime earnings.⁷⁴
 - Though trivial on an individual level, when applied across populations, neurotoxins have a significant impact. A loss of 5 points in IQ is of minimal significance in a person with an average IQ. However, a shift of 5 IQ points in the average IQ of a population of 260 million increases the number of functionally disabled by over 50% (from 6 to 9.4 million).⁷⁵
- **Findings from the recent research (targeted search):** Information reported in the following five studies contributed to the above-mentioned hypothesis.

Study #1: Sovikova E. Environmental risk factors in mental development of children. Toxicology Letters 2000;116:72.

Study #1 hypothesis being tested: Long-term exposure to lead and other metals causes deficits in cognitive functions of children.

Study #1 findings: Children living in areas with metallurgical plants performed worse on attention, memory, and intelligence tests than children in the control group. Additionally, the study found significant associations between lower cognitive ability level and unfavorable social and living environments (e.g., smoker in the family, lower income, lower family income, and nutritional problems, and lower education of mothers).

⁷³ Environmental Protection Agency. *Mercury White Paper*. Available at: <http://www.epa.gov/ttn/oarpg/t3/memoranda/whtpaper.pdf>.

⁷⁴ Ibid.

⁷⁵ Ibid.

Study #2: Myers GJ, Davidson PW. Does methylmercury have a role in causing developmental disabilities in children? *Environmental Health Perspectives* 2000;108(3):413-420.

Study #2 hypothesis being tested: Exposure to methylmercury during pregnancy can have adverse effects on the offspring's development.

Study #2 findings: Study findings show that exposure to methylmercury in very high doses causes developmental disabilities. Exposure to high levels of methylmercury, a potent neurotoxin, can result in developmental disabilities that can cause mental retardation, cerebral palsy, and seizures. However, impact from low dose exposure from fish has been difficult to demonstrate because of differences in developmental/neurological testing, study populations, endpoints, designated covariates, and statistical methods used across the studies reviewed. More research is needed to determine: 1) a more accurate way to measure the magnitude, duration, and timing of exposure; 2) whether peak or mean mercury levels should be used to determine brain exposure; 3) biomarkers; 4) the differences between low and high dietary exposure differ; 5) and the importance of age at the time of exposure.

Study #3: Sandborgh-Englund G, Ask K, Belfrage E, Ekstrand J. Mercury exposure in utero and during infancy. *Journal of Toxicology and Environmental Health* 2001;63:317-320.

Study #3 hypothesis being tested: Based on measured blood levels, in utero exposure to mercury is greater than postnatal exposure to mercury.

Study #3 findings: Mercury levels in cord blood of newly born infants were two times higher than maternal blood mercury levels. At the end of the sampling period, mercury level in infants had decreased more than 45%, even though the infants had been consuming breast milk with mercury levels. Thus, exposure to mercury in utero is more significant than during infancy. Due to a very limited number of observations, a more full scale study is needed.

Study #4: Carpenter DO. Effects of metals on the nervous system of humans and animals. *International Journal of Occupational Medicine and Environmental Health* 2001;14(3):209-18. (Note: This study is also cited under the research area of Biobehavioral Development.)

Study #4 hypothesis being tested: Metals such as methylmercury and lead have negative effects on nerve cells and neurobehavioral functioning, leading to developmental problems or an increased risk of neurodegenerative disease in old age.

Study #4 findings: Studies show that lead exposure in young children results in loss of IQ, shortened attention spans, and anti-social behavior. Low doses of methylmercury have been found to have effects on cognition, while high doses impede brain development. High levels of aluminum exposure result in dementia. The findings are inconclusive as to whether exposure to metals result in neurodegenerative disorders

such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Parkinson's disease.

Study #5: Carpenter DO. Effects of metals on the nervous system of humans and animals. International Journal of Occupational Medicine and Environmental Health 2001;14(3):209-18.

Study #5 hypothesis being tested: Metals such as methylmercury and lead have negative effects on nerve cells and neurobehavioral functioning, leading to developmental problems or an increased risk of neurodegenerative disease in old age.

Study #5 findings: Studies show that lead exposure in young children results in loss of IQ, shortened attention spans, and anti-social behavior. Low doses of methylmercury have been found to have effects on cognition, while high doses impede brain development. High levels of aluminum exposure result in dementia. The findings are inconclusive as to whether exposure to metals result in neurodegenerative disorders such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Parkinson's disease.

Hypothesis #24: In utero and postnatal exposure to lead has adverse effects on a child's neurodevelopment and biobehavioral development.

General Information Related to Hypothesis #24

- **Frequency/load of exposure:**
 - One million children in the US exceed the currently accepted threshold for blood lead level exposure that affects behavior and cognition (10micrograms/dl). Updating the toxic threshold to be consistent with recent studies would further lower this threshold.⁷⁶
 - Blood lead levels for children 6 and under have decreased by 75% between 1976 and 1991 due to elimination of leaded fuels and solder in food and drink cans.⁷⁷
- **Special Populations:** Though lead levels have significantly fallen, many U.S. children from low income families in older, urban, housing remain exposed.⁷⁸
- **Findings from the recent research (targeted search):** Information reported in the following three studies contributed to the above-mentioned hypothesis.

Study #1: Sovikova E. Environmental risk factors in mental development of children. Toxicology Letters 2000;116:72.

Study #1 hypothesis being tested: Long-term exposure to lead and other metals causes deficits in cognitive functions of children.

Study #1 findings: Children living in areas with metallurgical plants performed worse on attention, memory, and intelligence tests than children in the control group. Additionally, the study found significant associations between lower cognitive ability level and unfavorable social and living environments (e.g., smoker in the family, lower income, lower family income, and nutritional problems, and lower education of mothers).

Study #2: Nevin R. How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy. Environmental Research 2000;83(1):1-22. (Note: This study is also cited under the research area of Biobehavioral Development.)

Study #2 hypothesis being tested: Exposure to lead during the first three years of life causes adverse effects on cognitive abilities (measured by IQ tests), with positive correlations to such outcomes as unwed pregnancy and violent crimes.

Study #2 findings: Study findings support earlier research indicating that children with higher bone lead levels display more aggressive and delinquent behavior. Long-term trends in population exposure to gasoline and paint lead indicate that there is a strong association between exposure to lead and violent crimes and unwed pregnancy.

⁷⁶ Ibid.

⁷⁷ Ibid.

⁷⁸ Wasserman GA, Liu X, Pine DS, Graziano JH. Contribution of maternal smoking during pregnancy and lead exposure to early child behavior problems. Neurotoxicology and Teratology 2001;23(1):13-21.

Study #3: Carpenter DO. Effects of metals on the nervous system of humans and animals. *International Journal of Occupational Medicine and Environmental Health* 2001;14(3):209-18.
(*Note: This study is also cited under the research area of Biobehavioral Development.*)

Study #3 hypothesis being tested: Metals such as methylmercury and lead have negative effects on nerve cells and neurobehavioral functioning, leading to developmental problems or an increased risk of neurodegenerative disease in old age.

Study #3 findings: Studies show that lead exposure in young children results in loss of IQ, shortened attention spans, and anti-social behavior. Low doses of methylmercury have been found to have effects on cognition, while high doses impede brain development. High levels of aluminum exposure result in dementia. The findings are inconclusive as to whether exposure to metals result in neurodegenerative disorders such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Parkinson's disease.

Hypothesis #25: Exposure to lead impairs fetal biobehavioral development by lowering IQ and increasing cognitive developmental dysfunction.

General Information Related to Hypothesis #25

- **Prevalence and incidence:** Young children have the greatest risk in the first 3 years when cognitive abilities are developing. Effects of lead exposure in IQ appear most evident and predictive around 10 years of age. (Fraction of an IQ point is lost per 1ug/dl increase of blood lead.⁷⁹)
- **Cost to individual/family/society/healthcare system :**
 - Differences in IQ have been associated with difference in educational achievement and average lifetime earnings.⁸⁰
 - Though trivial on an individual level, when applied across populations, neurotoxins have a significant impact. A loss of 5 points in IQ is of minimal significance in a person with an average IQ. However, a shift of 5 IQ points in the average IQ of a population of 260 million increases the number of functionally disabled by over 50% (from 6 to 9.4 million).⁸¹
- **Frequency/load of exposure:** Blood lead levels for children 6 and under have decreased by 75% between 1976 and 1991 due to elimination of leaded fuels and solder in food and drink cans.⁸²
- **Special Populations:** Though lead levels have significantly fallen, many U.S. children from low income families in older, urban, housing remain exposed.⁸³
- **Findings from the recent research (targeted search):** Information reported in the following three studies contributed to the above-mentioned hypothesis.

Study #1: Nevin R. How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy. Environmental Research 2000;83(1):1-22.

Study #1 hypothesis being tested: Exposure to lead during the first three years of life causes adverse effects on cognitive abilities (measured by IQ tests), with positive correlations to such outcomes as unwed pregnancy and violent crimes.

Study #1 findings: Study findings support earlier research indicating that children with higher bone lead levels display more aggressive and delinquent behavior. Long-term trends in population exposure to gasoline and paint lead indicate that there is a strong association between exposure to lead and violent crimes and unwed pregnancy.

⁷⁹ Nevin R. How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy. Environmental Research 2000 May;83(1):1-22.

⁸⁰ Ibid.

⁸¹ Ibid.

⁸² Ibid.

⁸³ Wasserman GA, Liu X, Pine DS, Graziano JH. Contribution of maternal smoking during pregnancy and lead exposure to early child behavior problems. Neurotoxicology and Teratology 2001;23(1):13-21.

Study #2: Carpenter DO. Effects of metals on the nervous system of humans and animals. *International Journal of Occupational Medicine and Environmental Health* 2001;14(3):209-18.

Study #2 hypothesis being tested: Metals such as methylmercury and lead have negative effects on nerve cells and neurobehavioral functioning, leading to developmental problems or an increased risk of neurodegenerative disease in old age.

Study #2 findings: Studies show that lead exposure in young children results in loss of IQ, shortened attention spans, and anti-social behavior. Low doses of methylmercury have been found to have effects on cognition, while high doses impede brain development. High levels of aluminum exposure result in dementia. The findings are inconclusive as to whether exposure to metals result in neurodegenerative disorders such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Parkinson's disease.

Study #3: Sovikova E. Environmental risk factors in mental development of children. *Toxicology Letters* 2000;116:72. (*Note: This study is also cited under the research area of Neurodevelopment.*)

Study #3 hypothesis being tested: Long-term exposure to lead and other metals causes deficits in cognitive functions of children.

Study #3 findings: Children living in areas with metallurgical plants performed worse on attention, memory, and intelligence tests than children in the control group. Additionally, the study found significant associations between lower cognitive ability level and unfavorable social and living environments (e.g., smoker in the family, lower income, nutritional problems, and lower education of mothers).

Hypothesis #26: Maternally related factors such as smoking, exposure to environmental tobacco smoke, and substance abuse during pregnancy negatively affect biobehavioral development.

General Information Related to Hypothesis #26

- **Frequency/load of exposure:** In some urban areas of the U.S., an estimated 10-45% of pregnant women consume cocaine. An estimated 1/1000 newborns in the U.S. are exposed in utero to opiates.
- **Findings from the recent research (targeted search):** Information reported in the following three studies contributed to the above-mentioned hypothesis.

Study #1: Eskenazi B, Castorina R. Association of prenatal maternal or postnatal child environmental tobacco smoke exposure and neurodevelopmental and behavioral problems in children. *Environmental Health Perspectives* 1999 Dec;107(12):991-1000.

Study #1 hypothesis being tested: Environmental tobacco smoke (ETS) exposure to the fetus or child is associated with neurodevelopmental or behavioral effects. Specifically, there are adverse consequences to the child from maternal exposure to passive smoke during pregnancy or from the child's postnatal exposure to the smoke of others.

Study #1 findings: Active maternal smoking during pregnancy may be associated with negative effects on intellectual ability and behavioral problems. However, the impact of prenatal and postnatal ETS exposure is less clear. Animal and human data suggests that environmental tobacco smoke could cause subtle changes in child neurodevelopment and behavior. However, studies to date are difficult to interpret due to the influence of uncontrolled confounding factors, imprecision in measurements of smoking exposure, and co linearity of pre- and postnatal maternal smoking.

Study #2: Wasserman GA, Liu X, Pine DS, Graziano JH. Contribution of maternal smoking during pregnancy and lead exposure to early child behavior problems. *Neurotoxicology and Teratology* 2001;23(1):13-21.

Study #2 hypothesis being tested: There is an association between both maternal smoking during pregnancy and exposure to lead and behavioral development that is independent from social factors.

Study #2 findings: Adjusting for both social and average lifetime blood lead levels, prenatal smoking exposure proved to have significant increases in the total score on all testing subscales (e.g., aggressiveness, attention problems, thought problems) for children examined. Blood lead levels were shown to be significantly positively related to delinquency and to internalizing factors. Both maternal smoking and lead exposure are associated with childhood behavioral problems that continue into adulthood.

Study #3: Gressens P, Mesples B, Sahir N, Marret S, Sola A. Environmental factors and disturbances of brain development. *Seminars in Neonatology* 2001;6(2):185-94.

Study #3 hypothesis being tested: Fetal and neonatal brain development are influenced by environmental exposures to maternal and extra-maternal factors.

Study #3 findings: Studies demonstrate that exposure to ethanol, cocaine, anticonvulsants, viral infections, maternal diabetes, and untreated maternal phenylketonuria has a negative effect on brain development. It is highly likely that lead, heavy metals, benzodiazepines, and nicotine also have adverse effects on fetal brain development. There is a large variety of environmental factors and conditions that can interfere with fetal brain development, with maternal conditions representing a major source of factors. There is more need for controlled epidemiological studies addressing the impact of these factors and conditions. Also, there is a need to develop experimental models to better understand the real contribution and pathophysiological mechanisms of exposure effects on brain development.

Hypothesis #27: Broader societal factors such as neighborhood and community conditions can adversely impact a child's biobehavioral development.

General Information Related to Hypothesis #27

- **Findings from the recent research (targeted search):** Information reported in the following study contributed to the above-mentioned hypothesis.

Study #1: Caspi A, Taylor A, Moffitt TE. Neighborhood deprivation affects children's mental health: environmental risks identified in a genetic design. *Psychological Science* 2000;11(4):338-42.

Study #1 Hypothesis being tested: The neighborhoods in which children reside can exert a significant influence on the children's behavioral development beyond parental liability (e.g., selective migration) and heredity for behavioral or mental health problems.

Study #1 Findings: Study models indicated that children living in poor, neighborhoods ("neighborhood deprivation") have a small but significantly increased risk for behavioral problems, independent of any genetic predisposition toward mental or emotional problems. As such, neighborhood deprivation increases young children's behavioral and mental health problems. There is a need for additional studies to verify and document how these detrimental effects occur; study findings renew the impetus for community-level social intervention.